EXHIBIT A90

Articles

Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study

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Summary

Background Ovarian cancer is commonly fatal and incidence has persistently risen in Taiwan over the past 20 years. Prevention strategies, however, are limited. Pelvic inflammatory disease (PID) has been suggested to increase the risk of developing ovarian cancer, but the results of studies have been inconsistent. Therefore, we investigated whether PID increases the risk of developing ovarian cancer in a large, nationwide cohort.

Methods From the Longitudinal Health Insurance Database 2005 (LHID2005) in Taiwan, we obtained data for women aged 13–65 years for whom a diagnosis of PID, confirmed by multiple episodes, had been recorded between Jan 1, 2004, and Dec 31, 2005. We also obtained data for two controls per patient, matched for age and the year of first entry into the LHID2005. All patients were followed up from the date of entry in the LHID2005 until they developed ovarian cancer or to the end of 2006, whichever was earlier. We used Cox's regression models to assess the risk of developing ovarian cancer, with adjustment for age, comorbid disorders, and socioeconomic characteristics.

Findings We identified 67 936 women with PID and 135 872 controls. Among these 90 had developed ovarian cancer during the 3-year follow-up period (42 patients with PID and 48 controls, incidence 2·78 and 1·44 per 10 000 person-years, respectively). The adjusted hazard ratio for ovarian cancer in patients with PID was 1·92 (95% CI 1·27–2·92) compared with controls, which rose to 2·46 (1·48–4·09) in women who had had at least five episodes of PID. The adjusted hazard ratio was slightly higher for women aged 35 years or younger with PID than in older women with PID (2·23, 1·02–4·79 *vs* 1·82, 1·10–3·04).

Interpretation We found an association between PID and ovarian cancer. PID might, therefore, be a useful marker for ovarian cancer, and early treatment could help to improve prognosis. Whether pelvic inflammation itself accelerates the growth of ovarian cancers or affects cancer-cell differentiation in ways that adversely alter prognosis needs to be investigated.

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Introduction

Ovarian cancer is frequently fatal but prevention strategies are limited, partly because the causes of ovarian cancer remain obscure.[1,2] It is the second most common gynaecological cancer but has the highest mortality, and incidence increases with age.[3] In Taiwan the incidence has persistently risen over the past 20 years, and in 2006 the age-adjusted annual incidence per 100 000 women was 7·47; for comparison the average rate for western Europe and North America is ten cases per 100 000 and the lowest rate in Japan and in developing countries is five per 100 000.[4]

Although some progress has been made in prolonging remission by the combination of aggressive surgery and paclitaxel-based chemotherapy, outlook for patients with ovarian cancer remains poor, with 5-year survival being about 40%.[1] Possible reasons for the high mortality associated with ovarian cancer are the lack of early screening methods and difficulties in making a diagnosis.[1]

Epidemiological findings, including those from case-control[5–7] and cohort studies,[8] indicate that low parity, nulliparity, nulligravity, and infertility are important risk factors for ovarian cancer and are frequent complications of pelvic inflammatory disease (PID). In 1995, Risch and Howe[9] reported that PID increased the risk of epithelial ovarian cancer. Few other studies have been done, however, and the conclusions of those reported are inconsistent.[10,11] Thus, we did a large-scale, nationwide, controlled cohort study in Taiwan to investigate whether PID raises the risk of developing ovarian cancer.

Methods
Study population and study design

We obtained data from the Longitudinal Health Insurance Database 2005 (LHID2005), which is part of the Taiwan National Health Insurance Database, for women aged 13–65 years for whom a diagnosis of PID had been recorded between Jan 1, 2004, and Dec 31, 2005. PID was classified with the International Statistical Classification of Diseases and Related Health Problems (ICD) codes 614, 615, and 616 (ninth revision, clinical modification). Diagnoses of PID had been made on the basis of the patient's medical history, clinical features at presentation, and findings from bimanual palpation, ultrasonography, culture of vaginal samples, and laboratory data. Incompatible ultrasound images and negative results from commensal-bacteria culture ruled out PID.

We excluded patients who had only one record of PID between Jan 1, 2004, and Dec 31, 2005, and those without an identification number or date of birth. Additionally, we excluded patients who had been diagnosed as having ovarian cancer or a benign ovarian tumour (ICD codes 183 and 220) before 2004.

We created a control group from the remaining patients in the LHID2005. We excluded men, people with any record of PID from Jan 1, 2004, to Dec 31, 2005, and those without a recorded identification number or date of birth. We matched two controls to each PID patient, according to age (<30, 31–40, 41–50, 51–60, and >60 years) and the year of entry into the LHID2005. All patients and controls were followed up until they developed ovarian cancer (ICD code 183) or until Dec 31, 2006, whichever was earlier.

A diagnosis of ovarian cancer was based on the presence of a pelvic mass on imaging (CT, MRI, and ultrasonography) recorded in the LHID2005. The claims files include information on ambulatory care, inpatient care, sex, date of birth, and ICD codes. Since our study used anonymous secondary data from the LHID2005, it was exempt from full review by an independent review board.

Statistical analysis

To assess the risk of developing ovarian cancer up to 3 years after diagnosis of PID we did a multivariate survival analysis with Cox's regression models, with adjustment for confounding factors (age, monthly income, degree of urbanisation, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, and endometriosis). To meet the proportional hazards assumption, each dichotomous variable in the model was checked for proportionality by use of investigative diagnostic log–log survival plots. We used a bootstrap approach for sensitivity analysis because it is a robust method for validating Cox's regression models.[12,13] We did sensitivity analyses in the following patients: those with at least 6 months of follow-up; those with no diagnosis of ovarian cancer within the first 6 months; those aged 14–44 years (age range chosen in accordance with that in a previously published study[14] to exclude prepubescent girls and menopausal women, owing to the close relation between female hormone concentrations and PID); and those without endometriosis. Correspondence between the bootstrap hazard ratio (HR) and the median HR values was tested in 1000 replications, and the 95% CI was compared with the empirical 2·5 and 97·5 percentiles of the distribution of the HR. We calculated the ovarian cancer hazard function with the Kaplan-Meier method to assess the differences in the risk of ovarian cancer between the two cohorts. Finally, we calculated HRs (95% CI) for patients, according to age (≤35 years vs >35 years) and use of oral contraceptives (no history of use vs any previous use).

All data analyses were done with SAS (version 9.1.3). Significance was set at p=0·05.

	Patients with PID (n=67 936)	Controls (n=135 872)
Age (years)		
<18	1140 (1·7%)	2280 (1·7%)
18–30	21 779 (32·1%)	43 558 (32·1%)
31–40	20 330 (29·9%)	40 660 (29·9%)
41–50	15 856 (23·3%)	31 712 (23·3%)
51–60	5919 (8·7%)	11 838 (8·7%)
>60	2912 (4·3%)	5824 (4·3%)
Monthly income		
Financially dependent	17 269 (25·4%)	38 450 (28·3%)
NT$1–<16 000	8124 (12·0%)	17 568 (12·9%)
≥NT$16 000–32 000	33 799 (49·8%)	58 634 (43·2%)
≥NT$32 001	8744 (12·9%)	21 220 (15·6%)
Degree of urbanisation		
Urban	41 251 (60·7%)	86 372 (63·6%)
Suburban	19 831 (29·2%)	36 999 (27·2%)
Rural	6854 (10·1%)	12 501 (9·2%)
Endometriosis		
Yes	873 (1·3%)*	810 (0·6%)
No	67 063 (98·7%)	135 062 (99·4%)
Cardiovascular disease		
Yes	5770 (8·5%)*	10 743 (7·9%)
No	62 166 (91·5%)	125 129 (92·1%)
Diabetes mellitus		
Yes	2840 (4·2%)*	4423 (3·3%)
No	65 096 (95·8%)	131 449 (96·7%)
Chronic liver disease		
Yes	4015 (5·9%)*	4863 (3·6%)
No	63 921 (94·1%)	131 009 (96·4%)
Rheumatic disease		
Yes	921 (1·4%)*	1395 (1·0%)
No	67 015 (98·6%)	134 477 (99·0%)

PID=pelvic inflammatory disease. NT$=New Taiwan dollar. *p<0·0001 compared with controls

Table 1: Baseline variables for patients with PID and controls

	Patients with PID (n=67 936)	Controls (n=135 872)
Number of patients with ovarian cancer*	42	48
Incidence per 10 000 person-years	2·78	1·44
Crude HR (95% CI)	1·93 (1·27–2·91)	1·00
Adjusted HR† (95% CI)	1·92 (1·27–2·92)	1·00

PID=pelvic inflammatory disease. HR=hazard ratio. *Within 3 years of follow-up. †Adjusted for age, monthly income, degree of urbanisation, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, and endometriosis.

Table 2: Incidence and crude and adjusted risks of ovarian cancer

Role of the funding source

This study had no sponsor. The corresponding author had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results

We identified 68 668 women with PID, of whom we excluded 732 who had had ovarian cancer or a benign
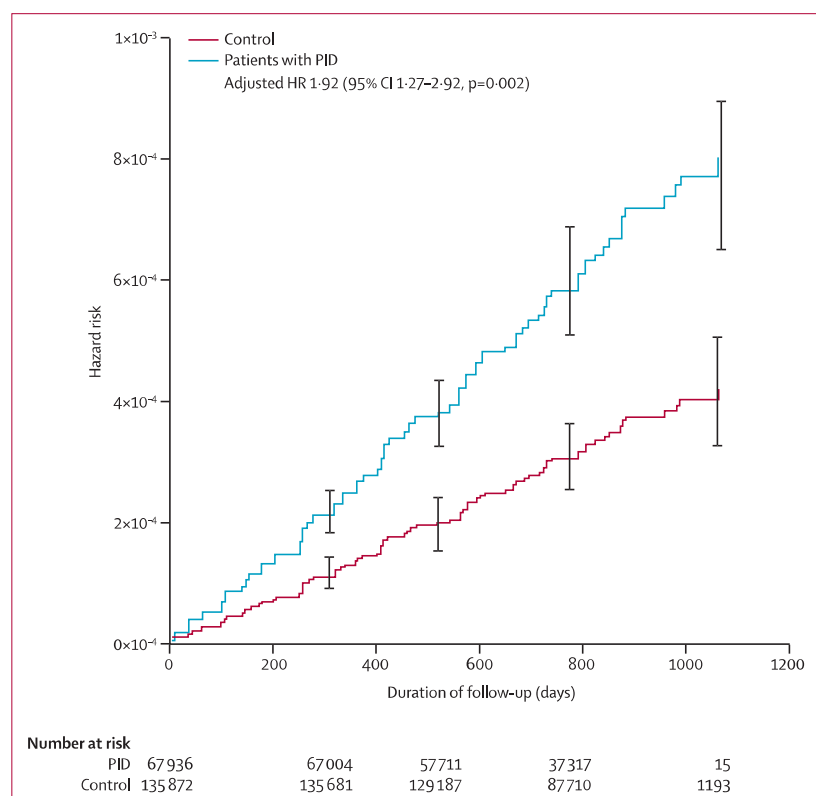
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Figure 1: Kaplan-Meier analysis of ovarian cancer risk in patients with PID and controls
95% CI and numbers remaining at risk are shown at 300, 550, 795, and 1100 days. PID=pelvic inflammatory disease. HR=hazard ratio.

	Ovarian cancer	No ovarian cancer	HR (95% CI)*
Primary analysis (within 3 years of follow-up)	42	67 894	1·90 (1·24–2·88)†
At least 6 months of follow-up and no ovarian cancer within first 6 months	30	67 906	1·60 (1·01–2·53)†
At least 6 months of follow-up, no ovarian cancer within first 6 months, and age 14–44 years	26	51 913	1·80 (1·01–3·10)†
At least 6 months of follow-up, no ovarian cancer within first 6 months, age 14–44 years, and no endometriosis	24	50 352	1·78 (1·01–3·19)‡

PID=pelvic inflammatory disease. HR=hazard ratio. *HRs and empirical 95% CI are derived from bootstrap analysis.
†Adjusted for age, monthly income, degree of urbanisation, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, and endometriosis. ‡Adjusted for all confounding factors except endometriosis.

Table 3: Bootstrap sensitivity analysis of Cox's regression model for risk of ovarian cancer in patients with PID

ovarian tumour before 2004. Thus, we assessed data for 67 936 PID patients and 135 872 controls. Characteristics at baseline are shown in table 1. Patients with PID had higher rates of comorbid endometriosis, cardiovascular diseases, diabetes mellitus, chronic liver disease, and rheumatic diseases than did controls (all p<0·0001).

The incidence of ovarian cancer was significantly higher in patients with PID than in controls (HR 1·93, 95% CI 1·27–2·91) and remained similar after adjustment (1·92, 1·27–2·92; table 2, figure 1). Among the 25 653 patients who had at least five episodes of PID, 22 developed ovarian cancer, compared with 48 controls

	No history of oral contraceptive use		History of oral contraceptive use	
	Patients with PID	Controls	Patients with PID	Controls
Diagnosis of ovarian cancer*				
Yes	39	47	3	1
No	65 871	134 533	2023	1291
Incidence per 10 000 person-years	5·92	3·49	14·81	7·74
Crude HR (95% CI)	1·86 (1·22–2·85)	1·00	2·03 (0·21–19·56)	1·00
Adjusted HR† (95% CI)	1·85 (1·21–2·85)	1·00	1·97 (0·17–23·36)	1·00

PID=pelvic inflammatory disease. HR=hazard ratio. *Within 3 years of follow-up.
†Adjusted for age, monthly income, degree of urbanisation, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, and endometriosis.

Table 4: Risk of ovarian cancer in patients with PID, according to use of oral contraceptives

	Age ≤35 years		Age >35 years	
	Patients with PID	Controls	Patients with PID	Controls
Diagnosis of ovarian cancer*				
Yes	14	13	28	35
No	33 462	65 849	34 432	69 975
Incidence per 10 000 person-years	1·898	0·812	3·626	2·008
Crude HR (95% CI)	2·29 (1·07–4·87)	1·00	1·80 (1·09–2·96)	1·00
Adjusted HR† (95% CI)	2·23 (1·02–4·79)	1·00	1·82 (1·10–3·04)	1·00

PID=pelvic inflammatory disease. HR=hazard ratio. *Within 3 years of follow-up.
†Adjusted for age, monthly income, degree of urbanisation, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, and endometriosis.

Table 5: Risk of ovarian cancer, according to age

(HR 2·46, 1·48–4·09). The sensitivity analyses for the Cox's model confirmed the risk of ovarian cancer in patients with PID when assessed by duration of follow-up, no ovarian cancer within 6 months, age, and presence of endometriosis (table 3).

The risk was significantly raised for patients with PID with no history of oral contraceptive use. For use of oral contraceptives, the risk of ovarian cancer was also raised, but not signficantly so and the risk was based on events in only three patients and one control (table 4).

In the different age-groups, the risk of ovarian cancer was slightly greater in patients aged 35 years or younger with PID than that in patients with PID who were older than 35 years (table 5). The differences between these age-groups, however, were not significant.

Discussion

Our data suggest that, after adjustment for potential confounding factors, the risk of ovarian cancer in women

with PID was almost double that in women without PID. To the best of our knowledge, this study is the first large-scale, nationwide cohort study to assess the relation between PID and risk of ovarian cancer.

A study done in Toronto, ON, Canada, by Risch and Howe[9] suggested that PID increased the risk of subsequent epithelial ovarian cancer. 104 (23%) of 450 cases and 102 (18%) of 564 controls with newly diagnosed ovarian cancer reported having had at least one episode of PID. Any PID was associated with an odds ratio (OR) of 1·53 (95% CI 1·10–2·13) and recurrent PID with an OR of 1·88 (1·13–3·12). An earlier population-based case-control study done in Shanghai, China, showed an OR of 3·0 (0·3–30·2) for women with a history of PID owing to infection, but only eight women with PID were assessed.[10] By contrast, a case-control study done in Milan, Italy, that involved 971 women with ovarian cancer and 2758 controls showed no increased risk of ovarian cancer in women with a history of PID (OR 0·7, 0·4–1·3). No confirmatory data have become available since that study (panel).

We extracted data from a large, nationwide database into which data are entered without selection bias: the LHID2005 contains information for 1 million beneficiaries enrolled in Taiwan's National Health Insurance pro-gramme, which in 2005 covered more than 98% of the Taiwanese population. Since a diagnosis of PID was already recorded according to ICD codes and each diagnosis was made by a physician, rather than being based on the patient's memory, misclassification bias is also unlikely. Additionally, each diagnosis of ovarian cancer had to be proven by biopsy and tissue pathology.

Women aged 35 years or younger who had PID were at slightly higher risk of developing ovarian cancer than were older women, although the difference between age-groups was not significant (table 5). This finding is similar to that of Risch and Howe,[9] who showed that the risk was raised in women with PID who were aged 20 years or younger compared with that in older women (≤20 years OR 3·08, 95% CI 1·17–8·13; 21–30 years 1·27, 0·79–2·05; >30 years 1·49, 1·00–2·23).[9] They also showed that the risk of ovarian cancer rose with increasing number of PID episodes, with relative odds of 1·36 (0·91–2·02) for one episode and 1·88 (1·13–3·12) for two or more. This finding supports our own of a notably raised risk in women who had had at least five episodes of PID. Hillis and colleagues[21] showed that among adolescents and women younger than 30 years the strongest predictor of recurrence of PID was infection with *Chlamydia trachomatis*; risk was raised two to eight times compared with that in women aged 30–44 years. Kelly and co-workers[22] also reported that among adolescent girls 47% had recurrent PID, probably because of high rates of sexual activity, poor use of protection and treatment, and vulnerable immune status. Thus, women with PID who are aged 35 years and younger might be at high risk of recurrent episodes of PID and, therefore, at notably raised risk of ovarian cancer.

Panel: Research in context

Systematic review

We searched PubMed for relevant articles, with the term "risk ovarian cancer AND pelvic inflammatory disease". We identified a study by Risch and Howe[9] that showed an association between PID and raised risk of developing ovarian cancer in 450 women aged 35–79 years in Toronto, ON, Canada (odds ratios 1·53 for any PID and 1·88 for recurrent PID). An earlier population-based case-control study done in Shanghai, China had also showed a relative risk of 3·0 for women with a history of PID, but data from only eight cases were assessed.[10] Other studies, however, have shown no increased risk of ovarian cancer. A case-control study done in Milan, Italy, in 971 women with ovarian cancer and 2758 controls, showed no increase in relative risk among those with a history of PID (relative risk 0·7). Likewise, a population-based case-control study done in the USA showed no increased risk in patients with PID (relative risk 0·9).[2] As no confirmatory data are available, we tested for heterogeneity with a meta-analysis (figure 2), which confirmed the inconsistency in reported results (p=0·009). Thus, we did a large, nationwide study based on data from a health insurance database.

Interpretation

Our study involved patients selected from a nationwide sample and in whom diagnoses of PID and ovarian cancer had been previously confirmed and reported according to ICD-9-CM codes. The risk of developing ovarian cancer was higher in patients with PID than in controls, especially in patients with PID who were aged 35 years or younger and in those who had recurrent PID.

With PID as a potential risk factor for ovarian cancer, in-depth assessment in patients with PID, including in those with comorbidities, such as cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, and endometriosis.[18–23] Further study should be done into the effects of use of oral contraceptives and whether pelvic inflammation and early preventive treatment against ovarian cancer in patients with PID can affect prognosis.

PID=pelvic inflammatory disease. ICD-9-CM=International Statistical Classification of Diseases and Related Health Problems, ninth revision, clinical modification.
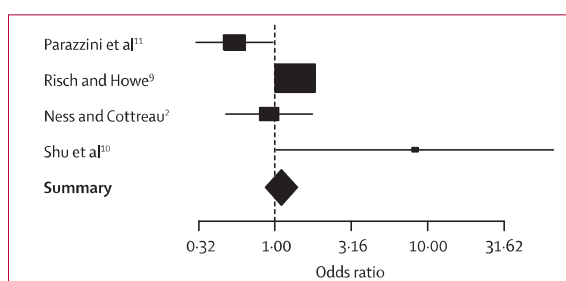
Figure 2: Meta-analysis of the odds ratio of ovarian cancer in women with PID in previously reported studies

Our population was Asian, whereas patients in previous studies have been mainly non-Asian. Differences in outcomes between ethnic groups have been noted by Aral and colleagues.[14] Among 7900 women aged 15–44 years, the proportion of white women with PID declined from 32·7% among those aged 30–34 years to 16·0% among those aged 40–44 years. By contrast, the percentages among African American women in the same two age-groups were similar (32·7% and 32·4%, respectively). The risks related to oral contraceptive use in Asian populations might differ notably from those in populations of other ethnic origins. Our finding was established in a group of

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women with confirmed PID, but owing to the limitations of the data in the LHID2005, we were unable to control for certain risk factors of ovarian cancer, such as parity, the use of hormone-replacement therapy or fertility medication, age of menarche and menopause, history of breastfeeding, and the lack of specific classification of types of PID and histological subtyping of ovarian cancer.

No history of oral contraceptive use was associated with raised risk of ovarian cancer, as expected. Unexpectedly, though, a history of oral contraceptive use also seemed to be associated with a raised risk. High use of oral contraceptives frequently correlates with high sexually activity,[23] which in turn could be associated with multiple occurrences of PID, and thereby increased risk of ovarian cancer. Nevertheless, the hazard ratios in our study were based on events in only three patients and one control and the difference risk was not significant.

Although in-vitro studies have shown that chronic inflammation can stimulate release of cytokines and chemokines that contribute to development or activation of malignant disease,[24] whether pelvic inflammation accelerates ovarian cancer growth in vivo or influences cancer-cell differentiation in ways that affect prognosis requires rigorous study. PID might constitute a marker for ovarian cancer that could enable early treatment and improved prognosis. The cutoff of follow-up at 3 years was, therefore, a limitation of the study. Further studies should adopt a longer follow-up period to validate the present findings.

Inflammation owing to bacterial or viral infection is a well reported precursor of human carcinogenesis. For instance, *Helicobacter pylori* is associated with gastric cancer human papilloma virus with cervical cancer, and hepatitis B and hepatitis C viruses with hepatocellular carcinoma. Whether infection affects the risk of developing ovarian cancer in patients with PID should be assessed. Even though the precursors of cancer vary by case, in previous studies inflammation has been purported as a potential biomarker of carcinogenesis.[25] Finally, as PID is potentially a pathogenic cause of ovarian cancer, chronic diseases associated with this disorder should not be neglected by clinicians—patients with diabetes mellitus,[15] endometriosis,[16] chronic liver disease,[17,18] rheumatic arthritis,[19] and cardiovascular disease[20] are at risk of comorbid PID.

Contributors
H-WL designed the study, analysed the data, and wrote the paper. Y-YT, SYL, W-JS, WLL, WZL, S-CW, and Y-LL interpreted the study results and wrote the discussion section of the paper. All the authors did literature searches.

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